a pertinent subset of the "Medicine" cluster of databases provided by STN (17 databases);

the Derwent Drug File (1983 - present) and the Derwent Drug Backfile (1964-1982) (previously known, collectively, as "Ringdoc");

and the Derwent World Patent Index;

and has discovered only the published studies or publicly available reports of clinical investigations, relevant to the use of teriparatide for treatment of osteoporosis in postmenopausal women and in men, which are discussed and cited elsewhere in the present application (see Application Summary, Section J). The cited documents, as published, are, in the opinion of Lilly, insufficient to support the approval of this application at least because they fail to provide any of the following:

a. randomized, double blind, placebo-controlled trial in women with postmenopausal osteoporosis, showing statistically significant reduction of both vertebral and non-vertebral fractures, and of back pain, by teriparatide alone (without concurrent anti-resorptive treatment such as hormone replacement therapy), as provided by Lilly study GHAC;

b. randomized, double blind, placebo-controlled trial in men between the ages of 30-85 years, with either hypogonadal or idiopathic osteoporosis, showing each of the following: statistically significant increases in bone mineral density (BMD) by the proposed dose of teriparatide alone (without concurrent anti-resorptive treatment such as 1,25-dihydroxyvitamin D); no gender differences with respect to safety, tolerability, or lumbar spine BMD responses to teriparatide, even though systemic response is lower in men than in women; and, hence, no dosage adjustment based on gender is required; each of which is provided by Lilly study GHAJ;

c. phase 2 study of dose-response relationship between markers of bone formation and common adverse events during 12 weeks of administration, showing teriparatide alone, in the dose range of 15 to 40 μg/day, to be safe and potentially effective in postmenopausal osteoporosis, as provided by Lilly study GHAA, and

d. six month follow up study after cessation of administration of teriparatide alone, in women with postmenopausal osteoporosis, as described in the above Lilly GHAC study, and in men with either hypogonadal or idiopathic osteoporosis, as described in the above Lilly GHAJ study, as provided by Lilly study GHBJ;

therefore, in Lilly's opinion, and to the best of Lilly's knowledge, the available published studies and publicly available reports do not provide a sufficient basis for the approval of the conditions for which Lilly is seeking approval without reference to the disclosures of the new clinical investigations in this application; and

3. the above clinical investigations were each conducted or sponsored by Lilly. Lilly was the sponsor named in the Form FDA-1571 of IND ——— which was submitted to the FDA on August 14, 1995 under which the new clinical investigations that are essential to the approval of this application were conducted.

Name of authorized official
Director, US Regulatory Affairs

16 November 2000
Date

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CERTIFICATION

NDA Application No.: 21-318

Drug Name: FORTÉO™

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: Gregory D Enas
Gregory G. Enas, Ph.D.

Title: Director, U.S. Regulatory Affairs

Date: November 21, 2000

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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 21, 2002

TO: Durand Hedin, Project Manager
Division of Endocrine and Metabolic
Drug Products, HFD-510

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: DSRCS Comments on Medication Guide for Forteo
NDA 21-318

Attached are the final comments you requested on the Forteo Medication Guide. Please let us know if you have any questions.

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Office of Drug Safety

Memo

To: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Kevin Dermanoski, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-400

Through: Denise Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support
HFD-400

Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-400

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
HFD-400

CC: Durand Hedin, RPh
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

Date: April 25, 2002

Re: ODS Consult 00-0262-01; Forteo [Teriparatide Injection (rDNA origin)]; NDA 21-318

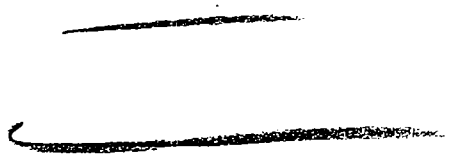
This memorandum is in response to the February 27, 2002 request from your Division for a re-review of the proprietary name, Forteo. We acknowledge the Division's decision to allow the sponsor to use the proprietary name "Forteo" despite DMETS' recommendation.

In our original consult, dated January 25, 2001, DMETS did not recommend the use of the proprietary name "Forteo." Although, we have not identified any additional concerns not stated in our initial consult that would render the name unacceptable, DMETS has continuing concerns regarding the potential risk of medication errors with the use of the proprietary name Forteo. Our concerns as stated in that review are briefly summarized below:

- The primary concern was related to three sound-alike, look-alike drugs that already exist in the U.S. marketplace, namely, Fortaz, Fiortal, and Tao. Although a slight potential for confusion does exist with Fortaz and Fiortal, a significant potential for confusion exists with the drug product Tao.

- DMETS conducted prescription studies that revealed, 56% (10 of 18) of the participants interpreted the verbal prescription as Tao. Additionally, 17% of the participants interpreted the verbal prescription as a phonetic variation of Fiortal. Overall, 83% of the verbal prescription study participants interpreted the name incorrectly. A repeat verbal prescription study revealed similar results for the product Tao. Fifty-five percent (6 of 11) of the participants misinterpreted the product as Tao. Although these studies involved a small sample size, a positive finding may indicate a high risk and the potential for medication errors when extrapolated to the general U.S. population.

Based on these concerns, DMETS does not recommend the use of the proprietary name Forteo. We would reconsider the acceptability of the name if the sponsor agreed to the following Phase 4 commitment:



If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

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/s/

Kevin Dermanoski
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PHARMACIST

Denise Toyer
5/1/02 04:34:29 PM
PHARMACIST

Carol Holquist
5/1/02 04:57:31 PM
PHARMACIST

Jerry Phillips
5/6/02 08:51:49 AM

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MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 9, 2002

TO: Durand Hedin, Project Manager
HFD-510

FROM: Karen Lechter, J.D., Ph.D.
Social Science Analyst
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety (ODS)

THROUGH: Anne Trontell, M.D., Director
Division of Surveillance, Research,
and Communication Support, HFD-410
Office of Drug Safety

SUBJECT: DSRCS User Manual Review for Forteo
_____NDA 21-318

The labeling that follows is a revised User Manual. We have proposed a few changes to make the document more user-friendly.

We already sent you this document by e-mail. Please let us know if you have any questions.

{See appended electronic signature page}

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/s/

Karen Lechter
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Anne Trontell
4/10/02 05:02:20 PM
MEDICAL OFFICER

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M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 15, 2002

TO: David Orloff, M.D., Director
Division of Endocrine and Metabolic Drug Products, HFD-510

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

FROM: Lois La Grenade, M.D., M.P.H., Epidemiologist, HFD-430
Division of Drug Risk Evaluation

SUBJECT: Consult: Evaluation of draft Post-Approval Surveillance Case Series Study submitted by the sponsor, with special emphasis on appropriateness of design.
Drug: Forteo (teriparatide)
Issue: Risk of osteosarcoma
PID#: D020056

Executive summary

This memorandum is in response to a consult request from Dr. Bruce Stadel, Division of Endocrine and Metabolic Drug Products, HFD-510, to review the draft protocol entitled "Teriparatide, Forteo™ Post-Approval Surveillance Study: Case Series (An Observational Study)". This has been submitted by the sponsor as part of a program to manage the possible risk of osteosarcoma in humans treated with Forteo™ (teriparatide), injectable biosynthetic human parathyroid hormone, intended for the treatment of osteoporosis. Forteo™ acts by stimulating new bone formation and in a pre-approval carcinogenicity study, rats treated with Forteo™ developed osteosarcoma, with a clear dose-response relationship. The agency has therefore decided that final approval should be dependent upon an adequate risk management program being in place, including a phase 4 study to investigate the possibility of an increased risk of osteosarcoma in humans treated with Forteo™.

ODS' opinion is that the case series method is **not** appropriate as rates cannot be calculated nor can inferences or conclusions be made from this type of study. It will add little if any new information to what we already know.

Background

This memorandum is in response to a consult request from Dr. Bruce Stadel, Division of Endocrine and Metabolic Drug Products, HFD-510, to review the draft protocol entitled "Teriparatide, Forteo™ Post-Approval Surveillance Study: Case Series (An Observational Study)", submitted by the sponsor. Forteo™ (teriparatide), injectable biosynthetic human parathyroid hormone, was issued an approvable letter by the agency in October 2001. It is intended for the treatment of osteoporosis and acts by stimulating new bone formation. In a standard 2-year carcinogenicity study in rats, the incidence of osteosarcoma was increased, in a dose-related fashion, with 0/120 tumors in the placebo group and ranged from 7/120 in the low dose treatment group to 53/120 in the high dose group. Another rat carcinogenicity study is in progress, but the agency has decided that final approval should be dependent upon an adequate risk management program being in place, including a phase 4 study to investigate the possibility of an increased risk of osteosarcoma in humans treated with teriparatide.

Draft Protocol Summary

To investigate the risk of osteosarcoma in patients treated with teriparatide, the sponsor proposes to conduct a "case series surveillance" study. The primary objectives will be to identify ~ 40% of newly diagnosed cases of osteosarcoma and to determine if any of these incident cases have a history of teriparatide use. The study will start 9 months after marketing and is to last for at least 5 years. Cases will be enrolled by active surveillance in selected oncology units. Consideration will be given to conducting a subsequent case control study if the case series study shows evidence of a possible association between osteosarcoma and teriparatide exposure.

Discussion

Appropriateness of Study Design

The design is inappropriate for the following reasons:

First, clinical case series investigations are generally used to describe new, unusual or unexpected clinical findings. Thus in pharmacoepidemiology case series investigations usually play a role in signal generation for adverse drug events. In this case, a signal has already been provided by the animal data. Furthermore a case series has no denominator, as there is no defined base population from which all cases are drawn, so rates cannot be calculated. . What is now required at this stage is analytic epidemiology studies, from which valid inferences can be

made as to whether or not there is an association between osteosarcoma and Forteo™ exposure. The case series method cannot do this as there would be no control group to which the proportion of cases exposed to Forteo could be compared.

Second, the proposed duration of the study is too short for the endpoint of cancer, which has a long latent period, usually decades. The study as proposed could conceivably have ended before any cases of Forteo ™ induced osteosarcoma presented for diagnosis.

A case series will therefore add little if any useful information to what is currently known.

Biological Plausibility

Osteosarcoma is one of a group of hormone-related cancers in which hormones (endogenous or exogenous) stimulate cell proliferation, thereby increasing the opportunity for accumulation of randomly generated genetic abnormalities, ultimately leading to carcinogenesis[1]. Other examples in this group include cancer of the breast, ovary, endometrium, prostate, testis and thyroid. The classic form of osteosarcoma usually occurs in patients in the second or third decade of life and is associated with the adolescent growth spurt[2]. Paget's disease of bone is a disorder characterized by alternating cycles of increased osteoblast and osteoclast proliferation and activity. Osteosarcoma is the commonest of sarcomas that develop in 5% - 10% of patients with polyostotic Paget's disease[3]. It is therefore not surprising that osteosarcomas developed in the rat carcinogenicity study, and conceivable that Forteo exposure might lead to an increased risk of osteosarcoma in humans. It should also be noted that the incidence of osteosarcoma in Paget's disease is several thousand-fold higher than the general population[4].

Special Problems of Cancer Epidemiology Studies

Cancer is a relatively rare event. There is a long latency period, i.e. a long period of time elapses between the exposure and the cancer becoming manifest. This makes it difficult to assess exposure after such a long time, as memories fade. There may be differential recall between cases and controls, leading to recall bias, and case ascertainment may be difficult with resultant selection bias. Ascertainment of risk and confounding factors is also difficult if done retrospectively. For rare exposures and outcomes, if restricted cohorts (restricted to the exposure) are not followed, the increase in risk from the exposure can be diluted and missed in the general population data.

Fletcher and Griffin[5] in 1991 observed that "for adverse reactions of long latency to be detected methods have to be used that permit observation of the patient to be followed for many months or years." They further made the point that this observation does not have to be continuous, but must allow for periodic contact with the patient.

Recommendations

In view of the concerns outlined above, the ideal study in this situation would be a cohort study, with enrollment of patients treated with Forteo™ and patients with a similar diagnosis, not treated with Forteo™, with prospective collection of data on exposure, other risk and confounding factors, and with periodic follow up for outcome information (development of osteosarcoma). However such a study would probably not be feasible, because of the large sample size required, the prolonged follow-up needed, and the expense of the study.

Instead we recommend as

Conclusions

In summary ODS' opinion is that the case series method proposed by the sponsor for assessing the risk of osteosarcoma with Forteo™ exposure is not appropriate and will do little to enhance current knowledge. Instead we recommend a mandatory registry of all Forteo™ exposed patients, with periodic follow-up over many years (10 – 20) for ascertainment of the incidence of osteosarcoma in the registry population and comparison to national estimates of osteosarcoma incidence. We think that this would provide the most accurate and timely estimate of whether or not there is an association between osteosarcoma and Forteo™ exposure, and is thus in the best interest of the public's health.

References

1. Henderson BE and Feigelson HS. Hormonal Carcinogenesis. *Carcinogenesis* 2000. 21 (3): 427-433
2. *Current Diagnosis and Treatment in Orthopedics* 2000. 2nd edition. p. 272
3. *Robbins Pathologic Basis of Disease* 1999. 6th edition, p.1227
4. Hansen MI, Nellissery MJ and Bhatia P. 1999. J Bone Miner Res. 14 Suppl 2:39-44
5. Fletcher AP and Griffin JP. International monitoring for adverse drug reactions of long latency. 1991. *Adverse Drug React. Toxicol. Rev.* 10 (4): 209-230
6. Honigfeld G. Effects of the Clozapine National Registry System on Incidence of Deaths Related to Agranulocytosis. 1996. *Psychiatric Services.* 47 (1): 52-56

Lois La Grenade, M.D., M.P.H.

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/s/

Lois LaGrenade
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MEDICAL OFFICER

Julie Beitz
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DIRECTOR

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CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: December 12, 2000	**DUE DATE:** March 9, 2001	**OPDRA CONSULT #:** 00-0262

TO: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Randy Hedin, Project Manager
HFD-510

PRODUCT NAME:	**DISTRIBUTOR:** Lilly Research Laboratories
Fortéo (Teriparatide Injection) rDNA origin **NDA #: 21-318**	

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

SUMMARY: In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA conducted a review of the proposed proprietary name "Fortéo" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

ODRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Fortéo".

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Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW:	**January 25, 2001**
NDA NUMBER:	**21-318**
NAME OF DRUG:	**Fortéo** **(teriparatide injection)**
NDA HOLDER:	**Lilly Research Laboratories**

I. INTRODUCTION

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the tradename "Fortéo", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Fortéo is the proposed proprietary name for teriparatide injection (rDNA origin) and is the first in the new class of bone formation agents. Once a day administration of Fortéo activates osteoblasts and stimulates the formation of new bone. Fortéo is indicated for the treatment of osteoporosis in postmenopausal women and in men. Fortéo should be administered as a subcutaneous injection into the thigh or abdominal wall; the recommended dosage is 20 mcg once a day. Each mL of solution contains 250 mcg of teriparatide therefore each 80 mcL dose delivers 20 mcg. The prefilled pen-injector which requires a single use, detachable and disposable pen needle (supplied separately) to function, is designed for self-injection and contains a 3 mL cartridge of teriparatide (rDNA origin). The pen-injector allows the patient to set (dial) a dose of 20 mcL for prime and 80 mcL for injection.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[i,ii,iii] as well as several FDA databases[iv] for existing drug names which sound-alike or look-alike to "Fortéo" to a degree where potential confusion between drug

[i] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

[ii] American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

[iii] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

[iv] COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[v]. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Fortéo". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- DDMAC did have concerns with the proposed drug name. DDMAC cited 21 CFR Sec 201.15(c) which states " All words, statements or other information required by or under authority of the act to appear on the label or labeling shall appear thereon in the English language: Provided however, that in the case of articles distributed solely in the Commonwealth of Peurto Rico, or in a Territory where the predominant language is one other than English, the predominant language may be substituted for English."

Four product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with Fortéo. The products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose	Other
Fortéo	Teriparatide injection (rDNA) (Rx)	20 mcg, once daily	
Fortaz	Ceftazidime 500 mg, 1 g and 2 g vial; 1 g and 2 g infusion pack; 6 g pharmacy bulk package; 1 g and 2 g ADD-Vantage Vial (Rx).	The usual adult dose is 1 gram administered IV or IM every 8 to 12 hours.	S/A, L/A per OPDRA
Fertinex	Urofollitropin 75 IU and 150 IU injection (Rx)	75 IU to 300 IU per day depending on the individual patient response	S/A, L/A per OPDRA
Fostex	Various preparations for dermatological use (Otc)	Varies depending on product	S/A, L/A per OPDRA
Fiortal	Aspirin 325 mg/Butalbital 50 mg/ caffeine 40 mg (Rx)	Adults: 1-2 tablets every 4 hours as needed	S/A, L/A per OPDRA

B. STUDY CONDUCTED BY OPDRA

1. Methodology

[v] WWW location http://www.uspto.gov/tmdb/index.html.

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of Fortéo with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 87 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for Fortéo (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Fortéo 20 mcg SQ daily #30	Forteo 20 mcg subcutaneously daily Dispense #30
Inpatient: Fortéo 20 mcg SQ QD	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Fortéo" response	Other response
Written: Outpatient	29	20 (70%)	5 (25%)	15 (75%)
Inpatient	30	13 (43%)	1 (8%)	12 (92%)
Verbal: Outpatient	28	18 (64%)	3 (17%)	15 (83%)
Total:	87	51 (59%)	9 (18%)	42 (82%)

Among the participants in the written prescription studies, 27 of 33 respondents (82%) interpreted the name incorrectly. The majority of the interpretations were misspelled variations of "Fortéo" such as *Fortco, Fostco, Fostio, Fostec, Fortto, Fosteo, Fosto, Fortsco*, and *Fortis*.

Among the verbal prescription study participants, 15 of 18 (83%) of the participants interpreted the name incorrectly. Majority of the incorrect name interpretations were phonetic variations of "Fortéo", such as *Forta, Fortail, Fortale* and *Fortel*. One participant provided *Tayl* as an interpretation. ***Ten participants*** interpreted the name as ***Tao,*** which is an approved drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

1. In reviewing the proprietary name " Fortéo ", the primary concerns raised were related to a few sound-alike, look-alike names that already exist in the U.S. marketplace. Three products, Fortaz Fiortal, and Tao were believed to be the most problematic in terms of potential medication errors. Tao was not discussed in the Expert Panel discussion as a concern, however the verbal prescription studies demonstrated that a significant potential for confusion does exist

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Fortéo could be confused with Tao, as ***ten study participants (56%) from the verbal prescription study provided Tao as an interpretation***. To confirm the results, OPDRA conducted a second verbal prescription study with a different group of healthcare professionals within FDA. Of the 11 responses from the second verbal prescription study, 6 participants (55%) provided Tao as an interpretation. As expected, the results confirmed our initial results in that Tao was being confused for Fortéo. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. Three study participants provided Fortail, Fortale, and Fortel as interpretations to the verbal study analysis. *These phonetic variations are very similar to the currently marketed drug name Fiortal.* The majority of the written prescription responses were phonetic variations of Fortéo.

Fortaz is the proprietary name for Ceftazidime, which is an antibiotic indicated for the treatment of patients with infections caused by susceptible strain organisms. Fortaz is available as a frozen, iso-osmotic, sterile, nonpyrogenic solution in vials containing 500mg, 1 g and 2 g of Ceftazidime, 1 g and 2 g infusion packs, 6 g pharmacy bulk pakage, 1 g and 2 g ADD-Vantage vials and 1g and 2 g plastic containers. The usual adult dosage is 1 g administered intravenously or intramuscularly every 8 to 12 hours. Fortéo and Fortaz do not sound similar but look similar when scripted as both names begin with the letter "Fort". Often when prescriptions are scripted the suffix of the name is scribbled making it difficult to discern the trailing letters. Fortéo differs from Fortaz in dosing interval, indication for use, and strength. Although the route of administration differs as well, post-marketing experience has demonstrated a large number of injections administered in routes other than indicated by the drug manufacturer. However, the fact that Fortéo will be available as a pen device and Fortaz is available in multiple strengths and preparations, diminishes the potential for confusion.

Fiortal is a nonnarcotic analgesic containing 325 mg of aspirin, 40 mg of caffeine and 50 mg of butalbital. An adult dose of one to two tablets every four hours is recommended. Three study participants provided Fortail, Fortale, and Fortel as interpretations to the verbal study analysis. These phonetic variations are very similar to the currently marketed drug name Fiortal. However,

given the differences in dosage form, dosing intervals, indication for use, and product administration, we believe the risk for confusion is relatively low.

Tao is the proprietary name for troleandomycin, which is a synthetically derived acetylated ester of oleandomycin. Tao is indicated for pneumococcal pneumonia due to susceptible strains and Group A beta-hemolytic streptococcal infections of the upper respiratory tract. Tao is available as a 250 mg capsule and is dosed as 250 mg to 500 mg four times daily. Although Fortéo and Tao do not look similar when scripted, the drug names do sound similar. The second syllable in Fortéo is similar to the full drug name of Tao. ***Ten out of eighteen study participants from the verbal prescription study provided Tao as an interpretation even though clarification on the route of administration and dosing was available.*** Many prescribers phoning in a prescription usually state the following: "I would like to call in a prescription *for* XX." The utilization of the preposition "for" (followed by the drug name) is often used when verbal orders are placed. In this case, this preposition could cause a potential problem because the order may be interpreted as Tao instead of Fortéo as was demonstrated by the verbal prescription study. In addition, Tao and Fortéo share similar numerical figures for product strength (i.e., 250 mcg/mL vs. 250 mg, respectively). Although Fortéo will be ordered in units, the possibility does exist where the product may be ordered in quantities of 3 or 4, as some prescription plans allow for a three month supply. Furthermore, when a prescriber verbally communicates an order for Fortéo, the pharmacist may assume that the prescriber is calling in *four* Tao tablets. Considering the results from the verbal prescription study and the similarities between Fortéo and Tao, the potential for confusion is significant.

2. Fortéo is similar to the English word "forte" which means strong. Numerous proprietary drug names in the U.S. marketplace utilize the "forte" as a modifier. Examples of these drug products include: Phrenilin Forte, Estrafon Forte, Invagesic Forte, Norgesic Forte, etc. Although a similarity does exist between Fortéo and the modifier, the fact that Fortéo stands alone as the proprietary name eliminates the possibility of confusion with the above listed proprietary names.

3. The accent mark utilized in the name Fortéo, implies that this name is not in English. OPDRA conducted a search of various languages (i.e. Spanish, French, Portuguese, and Italian) and discovered that Fortéo did not originate from any of the major languages. In addition, Jerry Phillips, Associate Director of OPDRA, contacted Bob Lee, a representative from Eli Lilly, to discuss where the proposed drug name originated. Bob Lee stated that the name Fortéo was created specifically for this drug product and is a fictitious name. Furthermore, OPDRA contacted Bob Temple for his opinion on the relevance of the regulation concerning the use of the English language. In Dr. Temple's opinion, the regulation, 21 CFR 201.15(c), is based on comprehensibility and does not apply to proprietary names that have no meaning.

III. LABELING, PACKAGING AND SAFETY RELATED ISSUES

In the review of the draft container label and draft package insert for Forteo, OPDRA has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvements, in the interest of minimizing potential user error and refer you to section IV.

IV. COMMENTS TO BE PROVIDED TO THE SPONSOR

OPDRA does not recommend the use of the proprietary name "Fortéo."

In reviewing the proprietary name " Fortéo ", the primary concerns raised were related to a few sound-alike, look-alike names that already exist in the U.S. marketplace. Three products, Fortaz Fiortal, and Tao were believed to be the most problematic in terms of potential medication errors. OPDRA conducted a review to assess the potential for confusion between Fortéo and Fortaz, Fiortal and Tao. Although a slight potential for confusion does exist with Fortaz and Fiortal, a significant potential for confusion exists with the drug product Tao.

We conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Fortéo could be confused with Tao, as ***10 out of 18 study participants (56%) from the verbal prescription study provided Tao as an interpretation***. To confirm the results, OPDRA conducted a second verbal prescription study with a different group of healthcare professionals within FDA. *Of the 11 responses from the second verbal prescription study, 6 participants (55%) provided Tao as an interpretation.* As expected, the results confirmed our initial results in that Tao was being confused for Fortéo. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

Although Fortéo and Tao do not look similar when scripted, the drug names do sound similar. The second syllable in Fortéo is similar to the full drug name of Tao. Many prescribers phoning in a prescription usually state the following: "I would like to call in a prescription *for* XX." The utilization of the preposition "for" (followed by the drug name) is often used when verbal orders are placed. In this case, this preposition could cause a potential problem because the order may be interpreted as Tao instead of Fortéo as was demonstrated by the verbal prescription study. In addition, Tao and Fortéo share similar numerical figures for product strength (i.e., 250 mcg/mL vs. 250 mg, respectively). Although Fortéo will be ordered in units, the possibility does exist where the product may be ordered in quantities of 3 or 4, as some prescription plans allow for a three month supply. Furthermore, when a prescriber verbally communicates an order for Fortéo, the pharmacist may assume that the prescriber is calling in *four* Tao tablets. Considering the results from the verbal prescription study and the similarities between Fortéo and Tao, the potential for confusion is significant.

LABELING, PACKAGING AND SAFETY RELATED ISSUES

1. CARTON LABELING

a. Per 21 CFR 201.100 (b)(2), the label shall bear "The recommended or usual dosage".

b. We recommend relocating the route of administration "For subcutaneous use" from the side panel to the primary display panel.

c. The term "ug" has been interpreted as "mg". We prefer the term "mcg" to be used throughout.

d. We recommend including the amount and strength each preset dose delivers such as "each 80 mcL delivers 20 mcg of teriparatide".

e. We prefer expressing the strength to read:

750 mcg/3 mL
(250 mcg/mL)

2. CONTAINER (PEN) LABEL

a. See comments above, as appropriate.

b. Since this Fortéo can only be utilized for 28 days after the first injection, the container label should also provide this information to the patient, especially since most people will refrigerate the pen device without the carton. We recommend placing a statement on the container label or pen device similar to the following:

May be used up to 28 days after first injection. Discard after _ _/_ _/ _ _

or

1st use _ _/_ _/_ _ Discard after _ _/_ _/ _ _

c. In the interest of not cluttering the label with unnecessary information, the word [redacted] may be omitted from the container label.

3. PACKAGE INSERT

The statement under INSTRUCTIONS FOR PEN USE in the package insert states "Each FORTÉO pen can be used for up to 28 days after the first injection. After the 28-day use period, discard the FORTÉO pen, even if it still contains some unused solution." We recommend summarizing (shortening) this statement so that it may be included on the carton labeling.

4. PEN DEVICE USER MANUAL

a. The statement "Your FORTÉO can be used for up to 28 days after the first injection pen. The FORTÉO pen should be properly disposed of after 28 days, even if it is not completely empty," which appears under the FOLLOWING INJECTION heading should also appear under the IMPORTANT NOTES heading so that reinforcement is provided for proper use.

b. We note that the pen must be primed before each use, however this statement is not clearly identified for the user. We recommend citing a bolded statement under the Priming the Pen heading which clearly instructs patients to prime the pen before each use.

5. PEN DEVICE

a. The IMPORTANT NOTES section describes the reasoning behind the placement of the numbers on the cartridge. It states that the numbers should be used to identify the amount of drug remaining in the cartridge. We recommend revising the numbers to present a clear and unambiguous description of the amount of drug remaining. Patients may not always remember the significance of the numbers or may not always have the user manual for reference. We recommend identifying the amount of drug remaining by stating the actual percentage remaining or used.

b. We have concerns that the pen device is not clearly marked to identify the difference between the numbers 1 and 2 on the dial set. We understand that the dial should initially be set to "1" to expel the primed dose and then set to "2" to administer the actual or intended dose. However, this information is not clearly marked on the syringe for patients who may not always have the User Manual available for reference (no correlation between 1 and priming has been established). Patients may not recall this information from the User Manual and may inadvertently administer the primed volume instead of the actual dose by dialing to the number 2 on the dial, in which case they will be under dosing. Patients may also inadvertently prime the actual dose and administer the actual dose in which case they will waste drug. In an effort to avoid confusion, we recommend establishing a direct correlation between what appears in the dose window and the intended dose for administration or volume for expulsion.

V. RECOMMENDATIONS

A. OPDRA does not recommend the use of the proprietary name "Fortéo".

B. OPDRA has recommended some labeling interventions that might minimize user error.

OPDRA would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3161.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Postmarketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Postmarketing Drug Risk Assessment (OPDRA)

APPEARS THIS WAY
ON ORIGINAL

/s/

Alina Mahmud
3/7/01 03:05:25 PM
PHARMACIST

Jerry Phillips
3/7/01 03:23:36 PM
DIRECTOR

Martin Himmel
3/13/01 04:02:51 PM
MEDICAL OFFICER

XI. Appendix

This section contains information regarding financial disclosure of investigators, examination of informed consent documents, and results of DSI investigations.

No irregularities were found in examination of informed consent documents. DSI investigations of two of the largest study sites also disclosed no irregularities.

APPEARS THIS WAY
ON ORIGINAL

Public Health Service
Food and Drug Administration

Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). 11/9/00

Clinical Investigators		
	See attached tables for each of the	"covered studies":
	B3D-MC-GHAC & B3D-MC-GHAJ	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Bruce H. Mitlak, MD	Medical Director
FIRM/ORGANIZATION: Eli Lilly and Company	
SIGNATURE: Bruce Mitlak	DATE: 9-NOV-00

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages Redacted 28

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Confidential,
Commercial Information

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-318

Eli Lilly and Company
Attention: Sunita Zalani, Ph.D.
Regulatory Research Scientist, U.S. Regulatory Affairs
Lilly Corporate Center
Indianapolis, IN 46285

Dear Dr. Zalani:

We acknowledge receipt on September 20, 2002, of your September 19, 2002 resubmission to your new drug application (NDA) for Forteo [teriparatide (rDNA origin)] Injection.

This resubmission contains a declaration that an inspection of the Lilly Technology Center in Indianapolis that manufactures Forteo drug substance was conducted on August 19, 2002, and that all manufacturing issues have been satisfactorily addressed in response to our May 16, 2002 action letter. We also note that you submitted the final report for a study entitled, "A Special Chronic Study in Female Fischer 344 Rats Given LY333334 (Teriparatide) by Subcutaneous Injection for up to 2 years" for review.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is March 20, 2003.

If you have any questions, call me at (301) 827-6392.

Sincerely,

{See appended electronic signature page}

Randy Hedin, R.Ph.
Senior Regulatory Management Officer
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Randy Hedin
10/1/02 10:19:44 AM

APPEARS THIS WAY
ON ORIGINAL

From: Hedin, Durand M
Sent: Friday, February 15, 2002 2:18 PM
To: 'ZALANI_SUNITA@LILLY.COM'
Subject: Pen Label, Carton Label, & User Manual comments

Dear Dr. Zalani,

We have the following comments concerning the pen label, carton label, and user manual for Forteo, NDA 21-318:

- Remove the accent mark from the name FORTEO in all places in the label.
- Change the generic name from. " [redacted] to "teriparatide (rDNA origin) injection" in all places in the label
- Insert the sentence, "Each cartridge is filled with 3.3 ml to deliver 3 ml." below the sentence that reads, "Preset dose: 20 mcg teriparatide subcutaneous once daily." on the carton label.
- Change the sentence on the carton label that reads, [redacted] ' to read, "Each mL, contains 250 mcg teriparatide (free base), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg metacresol, and Water for Injection."

Please contact me if you have any questions.

Randy Hedin

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/s/

Randy Hedin
2/15/02 03:32:34 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

Electronic Mail Message

From: Hedin, Durand M
Sent: Tuesday, October 16, 2001 9:05 AM
To: 'zalani_sunita@lilly.com'

Hi Sunita,

The following are comments from the Clinical Pharmacology and Biopharmaceutics review of Forteo Injection (NDA 21-318).

1. There are inconsistent values of essential pharmacokinetics parameters between noncompartmental and population approaches in Study LC-GHBI (Phase 1). The pharmacokinetic parameters derived from a conventional noncompartmental approach are more reliable than those from a population approach when their results are conflicted. In addition, extrapolated AUC from time zero to infinity showed significant overestimation after subcutaneous administration. Therefore, parameters such as apparent clearance and volume of distribution derived from extrapolated AUC are not acceptable in a noncompartmental method.

2. You did not conduct the effect of impaired hepatic function on teriparatide according to the Agency's guidance for the hepatic special population study. The impact of hepatic function was evaluated in the pivotal Phase 3 studies (LC-GHAC: Population PK/PD and GHAJ: Population PK). Based on the study report, patients with severe hepatic dysfunction were excluded from the study. The hepatic tests (the measurement of serum bilirubin, alanine transaminase, aspartate transaminase or gamma glutamyl transferase concentrations) in the patients with osteoporosis may not be adequate enough to define the association between hepatic function and disposition of teriparatide because the majority of patients in the study had normal ranges. Therefore, the study is not adequate.

The following is a summary of reviewers' comments on the questions raised by Lilly's Biopharm Team during a teleconference on September 29, 2001.

1. **Pharmacokinetic parameter estimation using population analysis (Study GHBI).**

Parameter estimation using population analysis with control file provided by the sponsor (refer to page 2) was not acceptable based on the following points:

A. The upper boundary conditions for bioavailability estimation significantly affected the output of the analysis.

B. Bioavailability and other pharmacokinetic parameters were estimated only with 20 ∝g SC using population analysis. An extension of the analysis to different doses (i.e., 40 and 80 ∝g SC) could confirm the appropriateness of the boundary conditions in the analysis. However, those were not conducted.

Therefore, the results of population analysis for the study were not validated and thus not acceptable.

2. **Drug interaction study between teriparatide and digoxin (Study GHBR)**

It is well known that digoxin PD change has about 1 week lag time compared to the digoxin plasma concentration change. To re-evaluate the digoxin-Forteo interaction study, The Agency should be provided with:

A. The digoxin plasma profile after single dose coadministration of teriparatide, or

B. PD evaluation after at least 7 days co-administration of teriparatide and digoxin.

If you have any questions please contact me.

Sincerely,

Randy Hedin

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/s/

Randy Hedin
10/16/01 09:30:29 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

Memo to File
NDA21-318 (Forteo™, teriparatide)
Reviewers: Jim Wei, Sung Chung

Re.: Correspondence to Teleconference

The following is summary of reviewers' comments on the questions raised by the Biopharm Team in Lilly regarding Forteo during the T-CON on Friday, SEP-29-2001.

1. Pharmacokinetic parameter estimation using population analysis (Study GHBI).

Parameter estimation using population analysis with control file provided by the sponsor (referring page 2) was not acceptable based on the following points:

1) The upper boundary conditions for bioavailability estimation affected significantly output of the analysis.
2) Bioavailability and other pharmacokinetic parameters were estimated only with 20 μg SC using population analysis. An extension of the analysis to different doses (i.e., 40 and 80 μg SC) could confirm the appropriateness of the boundary conditions in the analysis. However, those were not conducted.

Therefore, the results of population analysis for the study were not validated and thus not acceptable.

2. Drug interaction study between teriparatide and digoxin (Study GHBR)

It is well known that digoxin PD change has about 1 week lag time compared to the digoxin plasma concentration change. To re-evaluate the digoxin Forteo interaction study, tThe Agency should be provided with

1) The digoxin plasma profile after single dose coadministration of teriparatide, or
2) PD evaluation after at least 7 days co-administration of teriparatide and digoxin.

Clinical Pharmacology and Biopharmaceutics Team
DPE2/OCPB/CDER

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/s/

Xiao-xiong Wei
10/3/01 04:17:32 PM
BIOPHARMACEUTICS

MEMORANDUM

Date: September 6, 2001

To: NDA 21-318, Forteo™, Eli Lilly and Company

From: Yvonne Yang, Ph.D., Chemist Reviewer, HFD-510

Subject: Clarification for the consultation review by CDRH

This memo is to provide a clarification for the consultation review by CDRH. The CDRH review dated Mar-23-01 identified:

(1) Review: second paragraph, lines 3-4
"The pen injector for FORTEO is designed to administer fixed doses of **80 mcg**; the pen injector for ——

The 80 mcg (in bold) mentioned here should be 80 mcL (µl). The pen injector for FORTEO is designed to administer fixed doses of 80 mcL to deliver 20 mcg of teriparatide.

(2) Recommendation:
"Page 37 identifies the "2" setting as a 20 mcg dose, and that the pen is ready to inject. This is inconsistent with the dose, identified by a "2", being an **80 mcg** quantity, and other discussions that the **20 mcg** quantity is a priming, not dose, quantity."

The 80 mcg and 20 mcg (in bold) mentioned here are incorrectly quoted. The applicant has consistently stated in the application that the priming dose is 20 mcL (µl), and the injection dose is 80 mcL (µl), not mcg.

Cc: NDA # 21-318
HFD-510/Division file
HFD-510/Y Yang/DG Wu
HFD-510/R Hedin

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/s/

Yvonne Yang
9/6/01 09:31:02 AM
CHEMIST

Duu-gong Wu
9/17/01 10:19:55 AM
CHEMIST

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ON ORIGINAL